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# Asymmetric synthesis of methyl (2*R*,3*S*)-3-(4-methoxyphenyl) glycidate, a key intermediate of diltiazem, via Mukaiyama aldol reaction

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**Abstract**—Methyl (2*R*,3*S*)-3-(4-methoxyphenyl) glycidate, a key intermediate of diltiazem, was synthesized in good yield with high enantioselectivity based on chiral oxazaborolidine-mediated Mukaiyama aldol reaction of *p*-anisaldehyde with α,α-dichloro silyl ketene acetal (up to 96% ee), followed by reduction and cyclization. 

Diltiazem (**1**), a typical calcium antagonist, has been used throughout the world as a remedy for angina and hypertension.[1] Among the four possible stereoisomers of diltiazem, only the (+)-(2*S*,3*S*)-isomer exhibits potent coronary vasodilating activity. Therefore, diltiazem has been developed and marketed as a single isomer. For the synthesis of diltiazem, many processes have been extensively investigated, and at present diltiazem is mainly manufactured by the route using the optically active *trans* methyl glycidate (−)-**2** as a key intermediate (Fig. 1). Although a large number of synthetic approaches for the enantioselective synthesis of (−)-**2** have been reported,[2] for reasons involving enantiomeric purity and overall efficiency, more efficient methodology is needed. Recently, enzymatic preparation of (−)-**2** has been utilized in industrial production as an economical method.[3] However, there is a general drawback to the optical resolution in that the maximum yield of one enantiomer cannot exceed 50%, and, therefore a route to the asymmetric synthesis of (−)-**2** has been the focus of great attention. We report herein a novel asymmetric synthesis of (−)-**2** based on asymmetric Mukaiyama aldol reaction.[4]

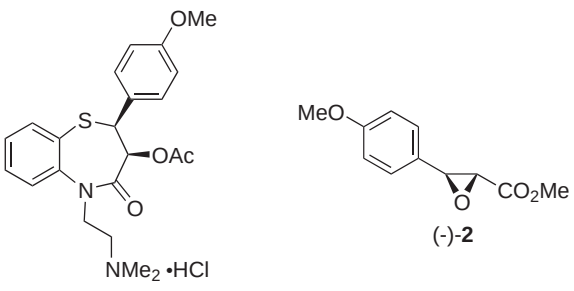
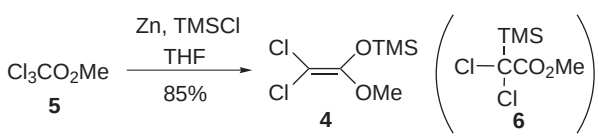



**Figure 1.**

For the introduction of the C-3 stereocenter of (−)-**2**, we envisioned the use of chiral Lewis acid-promoted Mukaiyama aldol reaction of *p*-anisaldehyde (**3**) with α,α-dichloro ketene silyl acetal **4**.[5] Generally, higher enantioselectivities are observed in the reactions with α,α-disubstituted ketene silyl acetals than in the reactions with an α-unsubstituted one in the asymmetric Mukaiyama aldol reaction.[6] Moreover, we expected that the reaction of **4** might proceed with high enantioselectivity, because high electronegativity and moderate bulkiness of the dichloro moiety could control its reactivity. Transformation of the resulting aldol product **8** to the *trans*-glycidate (−)-**2** has already been reported.[7]




**Scheme 1.**

*Keywords*: Mukaiyama reactions; asymmetric reactions; ketene acetals; sulfonamides.

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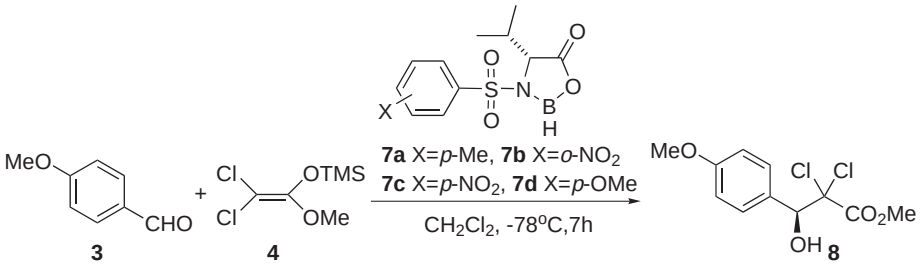
**Table 1.** Enantioselective Mukaiyama aldol reaction of *p*-anisaldehyde (**3**) with ketene silyl acetal **4** catalyzed by **7a–d**[a]




| Run | Catalyst (mol%) | **8** | |
|---|---|---|---|
| | | Yield (%)[b] | ee (%)[c] |
| 1 | **7a** (100) | 83 | 96 (>99)[d] |
| 2 | **7b** (100) | 89 | 93 |
| 3 | **7c** (100) | 83 | 89 |
| 4 | **7d** (100) | 30 | 88 |
| 5 | **7b** (20) | 88 | 77 |

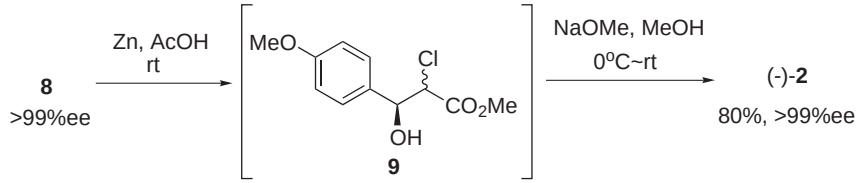
[a] Reactions were carried out with **3** (1.0 mmol) and **4** (1.5 mmol).
[b] Isolated yield after silica gel column chromatography.
[c] Determined by chiral HPLC (Chiralcel OJ, *n*-hexane:*i*-PrOH = 70:30, 230 nm, 0.6 ml/min, 35°C). The absolute configuration was determined as (*S*) by the retention time of HPLC (Ref. 2d).
[d] The ee value after single recrystallization from *n*-hexane–ether.

We began the present study by preparing the ketene silyl acetal **4**. As a practical method, we found that **4** was easily obtained from inexpensive starting materials: methyl trichloroacetate (**5**), zinc powder and TMSCl (Scheme 1).[8,9] To a suspension of **5** (17.7 g, 100 mmol) and activated zinc powder (9.8 g, 150 mmol) in THF (100 ml) was added dropwise TMSCl (15.2 ml, 120 mmol) at such a rate to promote gentle refluxing. Stirring was continued at ambient temperature for 30 min, then the reaction mixture was diluted with *n*-hexane and filtrated to remove the zinc salt. After evaporation of the solvent, the residue was distilled under reduced pressure (bp 64–65°C, 2 mmHg) to give **4** in 85% yield with no concomitant formation of α-silyl ester isomer **6**.

Next, we turned our attention to the asymmetric Mukaiyama aldol reaction. Several chiral Lewis acids, which are known to be excellent catalysts for the aldol reaction with chlorine-free ketene silyl acetals, were evaluated for their usefulness in the reaction of **3** with **4**. Among these catalysts, Kiyooka's chiral oxazaborolidine catalyst **7a**,[10] which was easily prepared by the sulfonamide obtained from D-valine with a $BH_3$·THF complex in $CH_2Cl_2$, has been shown to be capable of serving as an effective catalyst for the reaction (Table 1, Run 1).[11]

To a solution of **7a** (1.0 mmol) in $CH_2Cl_2$ (10 ml) were added successively **3** (1.0 mmol) in $CH_2Cl_2$ (1 ml) and **4** (1.5 mmol) in $CH_2Cl_2$ (1 ml) at −78°C, and the mixture was stirred at the same temperature for 7 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with AcOEt. After evaporation of the solvent, the resulting mixture was dissolved in THF (10 ml) and 1N aqueous HCl (2 ml) was added at room temperature. The reaction mixture was stirred for 30 min and extracted with AcOEt. After evaporation of the solvent, the residual crude product was purified by silica gel column chromatography to give the aldol product **8** as the desired (*S*) enantiomer in 83% yield and 96% ee (>99% ee after single recrystallization).

Although this reaction required a stoichiometric amount of catalyst, the greater part of it was readily recovered. Thus, acidification of the aqueous layer, followed by extraction with AcOEt, led to the recovery of the sulfonamide in 97% yield. While catalysts **7b** and **7c**, bearing an electron-withdrawing group in the arylsulfonyl moiety, also promoted the reaction in good




**Scheme 2.**

yields and with high enantioselectivities (Runs 2 and 3), the reaction using **7d**, bearing an electron-donating group, brought about a significant decrease of reactivity with similar enantioselectivity (Run 4). These differences in reactivity might be attributed to the Lewis acidity of the oxazaborolidine due to the substitution pattern of the sulfonamides. We also found that the reaction with a substoichiometric amount of **7b** (20 mol%) proceeded in 88% yield, but a somewhat lower enantiomeric excess of 77% was observed (Run 5). Although a clear mechanistic picture of the reaction has yet to emerge,[12] the stereochemical outcome of the reaction using **7** can be explained by Corey's model.[13]

Aldol product **8** thus obtained was easily converted to (−)-**2** according to the reported procedure.[7] Thus, **8** (>99% ee) was reduced to monochlorohydrin **9** on treatment with Zn in AcOH, which was treated with NaOMe in MeOH to give (−)-**2** (>99% ee) in 80% yield (Scheme 2).[14]

In summary, we have achieved a novel asymmetric synthesis of (−)-**2**, a key intermediate of diltiazem, based on chiral oxazaborolidine-promoted Mukaiyama aldol reaction of *p*-anisaldehyde (**3**) with α,α-dichloro ketene silyl acetal **4** (up to 96% ee), followed by reduction and cyclization. An efficient preparation of **4** from inexpensive starting materials has also been developed. Chiral *trans* glycidates and α,α-dichloro-β-hydroxy-esters are useful as versatile chiral building blocks for the synthesis of other pharmaceuticals and biologically active natural products.[15] Application of the present study to the synthesis of other useful chiral compounds is now being carried out.

## References


1. (a) Nagao, T.; Sato, M.; Nakajima, H.; Kiyomoto, A. *Chem. Pharm. Bull.* **1973**, *21*, 92–97; (b) Yasue, H.; Omote, S.; Takizawa, A.; Nagao, T. *Circ. Res. Supple. I* **1983**, *52*, 147.
2. For examples of the synthesis of (−)-**2** and its derivatives, see: (a) Yamamoto, M.; Hayashi, M.; Masaki, M.; Nohira, H. *Tetrahedron: Asymmetry* **1991**, *2*, 403–406; (b) Schwartz, A.; Madan, P. B.; Mohacsi, E.; O'Brien, J. P.; Todaro, L. J.; Coffen, D. L. *J. Org. Chem.* **1992**, *57*, 851–856; (c) Gentile, A.; Giordano, C.; Fuganti, C.; Ghirotto, L.; Servi, S. *J. Org. Chem.* **1992**, *57*, 6635–6637; (d) Matsuki, K.; Sobukawa, M.; Kawai, A.; Inoue, H.; Takeda, M. *Chem. Pharm. Bull.* **1993**, *41*, 643–648; (e) Chang, S.; Galvin, J. M.; Jacobsen. E. N. *J. Am. Chem. Soc*, **1994**, *116*, 6937–6938; (f) Takahashi, T.; Muraoka, M.; Capo, M.; Koga, K. *Chem. Pharm. Bull.* **1995**, *43*, 1821–1823; (g) Genet, J. P.; Androde, M. C. C.; Ratovelomanona-Vidol, V. *Tetrahedron Lett.* **1995**, *36*, 2063–2066; (h) Nanigia, A.; Rao, P. B.; Madhavi, N. N. L. *J. Chem. Research (s)* **1996**, 312–313.
3. Matsumae, H.; Douno, H.; Yamada, S.; Nishida, T.; Ozaki, Y.; Shibatani, T.; Tosa, T. *J. Ferment. Bioeng.* **1995**, *79*, 29–31.
4. For a recent review, see: Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357–389.
5. For examples of enantioselective Mukaiyama aldol reactions of halogen-substituted ketene silyl acetals, see: (a) Mikami, K.; Terada, M.; Nakai, T. *Tetrahedron: Asymmetry* **1991**, *2*, 993–996; (b) Iseki, K.; Kuroki, Y.; Asada, D.; Takahashi, M.; Kishimoto, S.; Kobayashi, Y. *Tetrahedron* **1997**, *53*, 10271–10280; (c) Iseki, K.; Kuroki, Y.; Kobayashi, Y. *Synlett* **1998**, 437–439; (d) Kiyooka, S.; Shahid, K. A.; Hena, M. A. *Tetrahedron Lett.* **1999**, *40*, 6447–6449; (e) Kiyooka, S.; Shahid, K. A. *Tetrahedron: Asymmetry* **2000**, *11*, 1537–1542.
6. Kiyooka, S. *Rev. Heteroatom. Chem.* **1997**, 245–270. Other related references are cited therein.
7. (a) Mukaiyama, T.; Murakami, M. *Chem. Lett.* **1981**, 1129–1132; (b) Ref. 2d.
8. Shchepin, V. V.; Efremov, D. I.; Desyatkov, D. A. *Zh. Obschch. Khim.* **1993**, *63*, 1283–1287.
9. Compound **4** was also prepared from methyl dichloroacetate, $Et_3N$ and TMSOTf. However, **4** was obtained in only poor yield and a considerable amount of the α-silyl ester isomer was produced.
10. Kiyooka, S.; Kaneko, Y.; Komura, M.; Matsuo, H.; Nakano, M. *J. Org. Chem.* **1991**, *56*, 2276–2278.
11. The Ti(IV)-Schiff base catalyst developed by Carreira et al. (Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994**, *116*, 8837–8838) and Ti(IV)–BINOL complex (Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1994**, *116*, 4077–4048) were not effective and gave poor yields.
12. For theoretical study on the coordination of aldehydes to *N*-sulfonyl oxazaborolidine, see: Salvatella, L.; Ruiz-López, M. F. *J. Am. Chem. Soc.* **1999**, *121*, 10722–10780 and references cited therein.
13. (a) Corey, E. J.; Rohde, J. J. *Tetrahedron Lett.* **1997**, *38*, 37–40; (b) Corey, E. J.; Barness-Seeman, D.; Lee, T. W. *Tetrahedron Lett.* **1997**, *38*, 4351–4354.
14. Optically pure (−)-**2** was also obtained from **6** (77% ee, Table 1, Run 5) in 58% yield after single recrystallization of the crude **2**.
15. (a) Rague, B.; Chapleur, Y.; Castro, B. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2063–2066; (b) Shono, T.; Kise, N. *Chem. Lett.* **1987**, 697–700; (c) Yamamoto, T.; Ishibuchi, S.; Ishizuka, T.; Haratake, M.; Kunieda, T. *J. Org. Chem.* **1993**, *58*, 1997–1998; (d) Flisak, J. R.; Gombatz, K. J.; Holmes, M. M.; Jarmas, A. A.; Lantos, I.; Mendelson, W. L.; Novack, V. J.; Remich, J. J.; Snyder, L. *J. Org. Chem.* **1993**, *58*, 6247–6254; (e) Boger, D. L.; Patane, M. A.; Zhou, J. *J. Am. Chem. Soc.* **1994**, *116*, 8544–8556; (f) Ruano, J. L. G.; Paredes, C. G. *Tetrahedron Lett.* **2000**, *41*, 5357–5361.